REMARKS

Claims 1-10, 14, and 15 are now pending. No new matter has been added. In many claims the definition of R^2 has been limited to hydrogen. In many claims R^4 is now defined as methyl or n-propyl. This narrower scope of claims clearly has utility as explained more completely below.

In the last Official Action, the Examiner stated that claims 1-6 and newly added Claims 7-13 were rejected under 35 U.S.C. § 101 arguing that the claimed invention was not supported by either a specific or substantial asserted utility or a well established utility.

On page 4, lines 4-6 in the last Office Action, the Examiner stated that the 5-methylproline methyl ester has a specific utility as found in EP 0 618 926, while the 5-(n-propyl)proline methyl ester has no stated specific or substantial utility. The Examiner also stated that the production of 5-(n-propyl)proline methyl ester does not provide support for a specific and substantial utility since no utility is given for this intermediate and the pharmaceutical products and agricultural compounds are still not given in examples and a direction for use of the final products is not given.

The attention of the Examiner is respectfully invited to Cossy et al "Synthesis of (-) Pseudoconhydrine through Ring Enlargement of an L-Proline Derivative; SYNLETT, August 1997; pages 905 and 906 a copy of which is attached hereto and is

labeled Exhibit A.

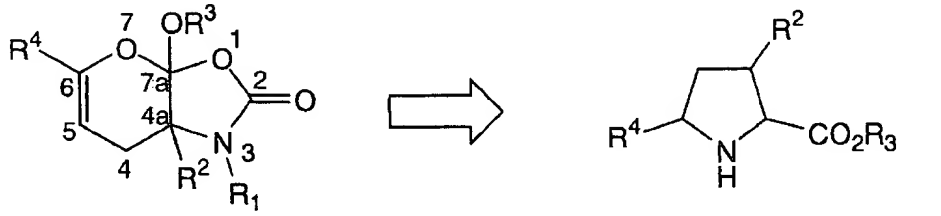
Exhibit A shows that the 5-(n-propyl)proline methyl ester, produced in the Additional Reference Example in the document entitled "DECLARATION UNDER 37 CFR 1.132" dated October 23, 2002, and filed in this case on October 30, 2002, (The Miyata declaration), has a specific and substantial utility.

Exhibit A shows that 1-benzoyl-5-(n-propyl)proline methyl ester (N-benzoyl form) serves as a synthetic intermediate (shown as the compound 4+4' in Scheme 1) for producing "(-)-pseudoconhydrine", which is shown to have biological properties, as an alkaloid. Said 1-benzoyl-5-(n-propyl)proline methyl ester can be easily obtained, by treating the 5-(n-propyl)proline methyl ester with benzoyl chloride in the presence of a base. Exhibit A clearly proves that the compound, 5-(n-propyl)proline methyl ester, has a specific and substantial utility.

In the current claims, R^2 is hydrogen and R^4 is a methyl group or a n-propyl group. Considering the wording of the current claims and the showing of utility for the 5-(n-propyl)proline methyl ester, it is clear that all pending claims are directed to subject matter clearly having utility and fully meeting the requirements of 35 U.S.C. § 101.

The attention of the Examiner is invited to the following reaction showing how each of the substituents finds its way into the final product. Please note that from the *final* product shown below, R^3 will leave by hydrolysis to form a 5-methylproline

methyl ester or 5-(n-propyl)proline methyl ester, for which the utility is clearly shown. This reaction clearly demonstrates the utility of all claimed subject matter consistent with arguments previously made in this case.



Claimed Compound

5-substituted proline ester

Summary

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact David R. Murphy (Reg. No. 22,751) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,
BIRCH, STEWART, KOLASCH & BIRCH, LLP

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Exhibit A: Cossy et al "Synthesis of (-) Pseudoconhydrine through Ring Enlargement of an L-Proline Derivative; SYNLETT, August 1997; pages 905 and 906.

APP # 09/988,042

Synthesis of (-)-Pseudoconhydrine through Ring Enlargement of a L-Proline Derivative

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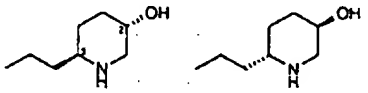
Abstract : A short synthesis of (-)-pseudoconhydrine is described from L-proline by using a ring enlargement reaction.

Alkaloids possessing the piperidin-3-ol system are abundant in nature and many of them have interesting biological properties.[1] Since its isolation from *Conium maculatum* L.[2] (Umbelliferae), the absolute configuration of (+)-1 has been established to be (2*S*,5*S*) based on Hoffman degradation.[3] (+)-Pseudoconhydrine has been of special interest for many research groups. The synthesis of 1 has been reported several times in its racemic form[4] and enantiomerically enriched form[5] (+)-1 as well as (-)-1.[6]

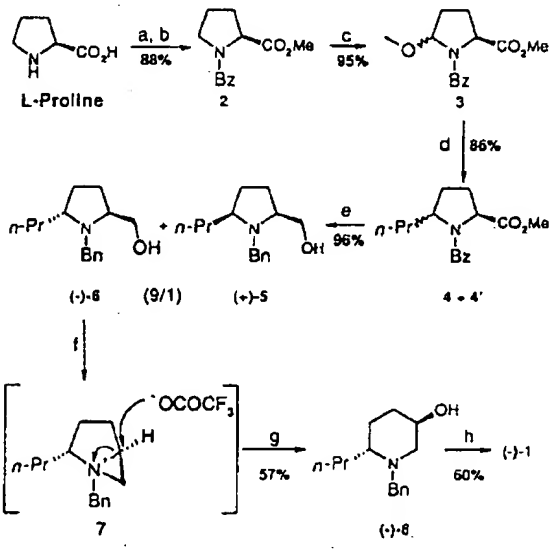


(+)-1 (-)-1

In connection with our program directed towards the selective synthesis of 3-hydroxypiperidines through ring enlargement of prolinol[7], the synthesis of (-)-1 has been achieved starting from the commercially available inexpensive L-proline.

N-Benzoyl L-proline (obtained by treatment of L-proline with benzoyl chloride in 1.25 M aqueous NaOH) reacted with K_2CO_3 and then with MeI to afford the methyl *N*-benzoylprolinate **2**[8] (88% overall yield). Anodic oxidation[9] of **2** (15.4 mmol) in methanol (15 mL) containing a catalytic amount of tetraethylammonium *p*-toluenesulfonate provided the methyl *N*-benzoyl-5-methoxyprolinate **3**[10] as a mixture of two separable stereoisomers in a 1:1 ratio (95%). Displacement of the methoxy group of **3** with a *n*-propyl group was achieved on treating **3** with one equivalent of *n*-PrMgBr, CuBr·Me_2S and BF_3·Et_2O in Et_2O.[11] This led to a 9:1 mixture of non-separable isomers **4** and **4'**. Reduction of this mixture with $LiAlH_4$ in THF produced the 1-benzyl-5-propylpyrrolidine-2-methanol (+)-**5** and (-)-**6** in a 1:9 ratio (96%) which were separated by flash chromatography on silica gel.[12] Treatment of 1-benzyl-5-propylpyrrolidine-2-methanol (-)-**6** with trifluoroacetic anhydride in THF followed by addition of NEt_3 and then addition of an aqueous solution of NaOH (2.5 M) gave piperidin-3-ol (-)-**8**[13,14] (57%) which has the pseudoconhydrine skeleton. The relative configuration of the hydroxy and the *n*-propyl groups was established by ^{1}H NMR spectrum and NOE experiments. Debenzylation was achieved by hydrogenolysis in the presence of $Pd(OH)_2$ (1 atm, H_2, 16 h, yield: 60%). This liberated (-)-pseudoconhydrine (-)-**1**, the structure of which was confirmed by addition of dry HCl and crystallisation of the hydrochloride salt from Et_2O which had spectral data, melting point (205 °C) and $[\alpha]_D^{20}$ = -6 (*c* = 1.05, MeOH) similar to reported data in the literature.[5b]

In summary, we have realized a short synthesis of (-)-pseudoconhydrine [(-)-**1**] from L-proline based on a stereospecific prolinol/piperidin-3-ol rearrangement[7], a reaction which is consistent with the formation of a 1-azabicyclo[3.1.0]hexane intermediate **7** through S_Ni solvolysis of the primary alcohol of the prolinol (-)-**6** (participation of the amino moiety to the isomerization).



a) PhCOCl, NaOH; b) MeI, K_2CO_3; c) -2e , MeOH, Et_4NTs; d) *n*-PrMgBr, CuBr.Me_2S, BF_3.Et_2O; e) $LiAlH_4$, THF; f) i:$(CF_3CO)_2O$, ii:NEt_3; g) NaOH; h) H_2, $Pd(OH)_2$, MeOH.

Scheme 1

Acknowledgement

We thank Dr H. Dhimane for his help in anodic oxidation, C. Chassagnard for NOE experiments and Dr. J-L. Ranaivosata for providing the ^{1}H NMR spectra of compound (+)-**8**.

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(12) The flash chromatography eluent was CH_2Cl_2/MeOH/NH_3: 95/5/0.1.

(13) For compound (+)-8 see Ref. 5c.

(14) Trifluoroacetic anhydride (56 µL, 0.40 mmol, 1.1 eq.) was added dropwise to a solution of (-)-6 (85.2 mg, 0.36 mmol, 1 eq.) in THF (5 mL) cooled to -78 °C and under inert atmosphere. After 3 hours triethylamine (0.19 mL, 1.37 mmol, 3.8 eq.) was added dropwise at -78 °C. The reaction mixture was stirred for 15 minutes at -78 °C and then refluxed for 3 days. After addition of sodium hydroxide (2.5 M, 2 mL), the mixture was stirred for 1 hour then extracted by dichloromethane (3x5 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The oil was purified by flash chromatography on alumina (Merk aluminium oxide 90, 0.063-0.200 mm) eluent (ethyl acetate/cyclohexane : 50/50).

(-)-8: oil; $[\alpha]_D^{20}$ = -43 (*c* = 2.06, EtOH). IR (NaCl): 3360, 2940, 1500, 1020 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, ^3J=9.0 Hz, 3H), 1.10-1.63 (m, 6H), 1.67-1.83 (m, 2H), 1.97 (dd, ^2J=11.3 Hz, ^3J=8.1 Hz, 1H), 2.19-2.46 (m, 2H), 2.75 (dd, ^2J=11.3 Hz, ^3J=2.5 Hz, 1H), 3.34 (d, ^2J=13.3 Hz, 1H), 3.63-3.70 (m, 1H), 3.86 (d, ^2J=13.3 Hz, 1H), 7.07-7.28 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.4 (CH_3), 19.1 ($2CH_2$), 26.4 (CH_2), 30.8 (CH_2), 56.7 (CH_2), 57.7 (CH_2), 58.9 (CH), 66.3 (CH), 126.8 (CH), 128.1 (2CH), 128.8 (2CH), 139.0 (C). MS (CI, CH_4) *m/z*: 234 ($M+H^+$,100), 216 (60), 190 (92), 147 (16), 91 (16). HMRS calculated for $C_{15}H_{24}NO$: 234.1857, found : 234.1856.